

Docket No. 434-263

**CATALYTIC CLEAVAGE OF PHOSPHATE ESTER BONDS
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This application claims the benefit of U.S. Provisional Patent
Application Serial No. 60/445,985 filed February 7, 2003.

Technical Field

The present invention relates to compositions and methods for cleavage of phosphate ester and ether bonds. In particular, the invention relates to a chelating ligand comprising a Group 13 element and a halide, and 5 to methods for using the ligand for dealkylation of a phosphate ester or an ether.

Background of the Invention

It is known that the breaking of a phosphate ester bond is an important 10 step in the destruction of chemical warfare agents such as Sarin gas and VX, in the destruction of pesticides such as chlorpyrifos, and in other biological systems. Such compounds irreversibly block a serine hydroxy group in the cellular enzyme acetylcholinesterase by phosphorylation, thereby disrupting the cells' neurological function. Accordingly, substantial effort has been

devoted to development of methods for decontamination of such nerve agents and pesticides. The cleavage of the P-O-C bond in such nerve agents/pesticides has been targeted as a method of decontamination. Many such methods use d-block metals such as cobalt, copper, and zinc. It is also 5 known to destroy nerve agents by hydrolyzing them using basic solutions and/or bleach to oxidize them to less toxic inorganic phosphates and alkali. However, these solutions are caustic and should only be handled under carefully controlled conditions. Large excesses of bleach and/or bases are required for successful decontamination, and the active agent (chlorine) in 10 bleach decreases with time. Further, bases and bleach are not selective for nerve agents, and readily undergo undesirable and potentially explosive side reactions.

Similarly, methods are known for breaking the C-O-C bond in ethers such as methyl tertiary butyl ether (MTBE) to prevent, for example, 15 contamination of groundwater thereby. Prior art methods include cleavage by hydrogen halides, organic acids, amines/amine salts, sulfonyl halides, inorganic acid anhydrides, Lewis acid halides, Grignard reagents, and alkali metal alkyls. The modes of action of these reagents are varied, including elimination, substitution, and oxidative cleavage. Further, it is known to 20 cleave MTBE by concentrated acid. However, concentrated acid also risks contamination of the environment, and the rate of hydrolysis is slow when dilute aqueous acid is used to avoid contamination. Biodegradation of MTBE is slow under anaerobic and aerobic conditions using conventional methodology, and certain methods such as gas phase catalytic oxidation of

MTBE require high temperatures.

There is accordingly identified a need in the art for a successful deactivating/destroying agent for such toxic nerve agents as nerve gas (Sarin gas, VX, and the like) and organophosphate pesticides. Such an agent should
5 be easily synthesized from inexpensive reagents, should be soluble in the same solvents as the nerve gases/pesticides, will preferably be selective for the nerve agents, will not readily undergo unwanted side effects upon reaction with the nerve agents, and will be substantially non-toxic.

Summary of the Invention

10 In accordance with the foregoing, a new class of chelating ligands have been synthesized which serve as catalysts for the dealkylation of phosphate ester and ether bonds. Each ligand comprises a Group 13 element and a halide. While not wishing to be bound by any theory, when combined with a molecule containing a phosphate ester bond or an ether bond, it is
15 believed that the ligand undergoes dissociation of a halide which then attacks a carbon atom of the bond being broken, thereby cleaving the bond.

In one aspect of the invention a chemical compound is provided, comprising the general formula $L\{YX_m\}_n$. X may be selected from the Group 13 elements consisting of boron, aluminum, gallium, indium, and tellurium.
20 Y may be selected from the halide group consisting of fluorine, chlorine, bromine, iodine, and astatine. L is typically a chelating ligand containing at least one binding atom contacting the Group 13 element, the atom selected from the group consisting of C, N, O, and S, and m and n are integers having

a value of at least 1.

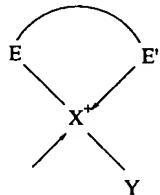
In another aspect, L may be a Schiff base-containing ligand. X may be selected from the Group 13 elements consisting of boron, aluminum, gallium, indium, and tellurium, and Y may be selected from the halide group consisting of fluorine, chlorine, bromine, iodine, and astatine. In one embodiment, L may be a salen ligand which is bidentate, quadridentate, or greater. Typically, L is selected from the group consisting of Salen ('Bu), Salpen ('Bu), Salben ('Bu), and Salhen ('Bu).

In yet another aspect, a method is provided for dealkylation of a phosphate ester or an ether, comprising contacting the phosphate ester or ether with a compound comprising the general formula $L\{YX_m\}_n$ as described above. As described, L is typically a salen ligand, Y is typically boron or aluminum, and X is typically chlorine, bromine, or iodine.

In still yet another aspect of the present invention, a catalytic method for dealkylation of a phosphate ester or an ether, comprising contacting the phosphate ester or ether with the compositions as described above in the presence of BBr_3 . The phosphate ester or ether and BBr_3 may be added in equimolar amounts. Typically, the dealkylation reaction using the compositions and methods of the present invention is conducted at ambient temperature. Addition of an excess of BBr_3 renders the reaction catalytic, allowing regeneration of the original composition and continuation of the reaction.

Yet still further, the present invention provides a catalytic method for dealkylation of a phosphate ester or an ether, comprising contacting the

- phosphate ester or ether with a compound comprising the general formula $L\{YX_m\}_n$ wherein X is selected from the Group 13 elements consisting of boron, aluminum, gallium, indium, and tellurium, Y is selected from the halide group consisting of fluorine, chlorine, bromine, iodine, and astatine,
- 5 L is a chelating ligand containing at least two molecules E and E' contacting the Group 13 element, the molecules E and E' being selected from the group consisting of C, N, O, and S, and m and n are integers having a value of at least 1. Typically, the compound generates a cationic intermediate upon contacting the phosphate ester or ether, the cationic intermediate having the
- 10 general formula:



- As described above, L may be a Schiff base-containing ligand, such as a salen ligand. L may be a bidentate ligand, a quadridentate ligand, or greater. In one embodiment, L is selected from the group consisting of Salen ('Bu), Salpen ('Bu), Salben ('Bu), and Salhen ('Bu). The reaction is rendered catalytic by conducting it in the presence of BBr_3 . The phosphate ester or ether and BBr_3 may be added in equimolar amounts. The dealkylation reaction may be conducted at ambient temperature.
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Other objects of the present invention will become apparent to those skilled in this art from the following description wherein there is shown and

described a preferred embodiment of this invention, simply by way of illustration of the modes currently best suited to carry out the invention. As it will be realized, the invention is capable of other different embodiments and its several details are capable of modification in various, obvious aspects all without departing from the invention. Accordingly, the drawings and descriptions will be regarded as illustrative in nature and not as restrictive.

Brief Description of the Drawing

The accompanying drawings incorporated in and forming a part of the specification illustrates several aspects of the present invention and, 10 together with the description, serves to explain the principles of the invention.

In the drawing:

Figure 1 is a structural depiction of a bidentate ligand according to the present invention, wherein X is a halide;

15 Figure 2 is a structural depiction of a quadridentate ligand according to the present invention, wherein X is a halide and L is a quadridentate Schiff base ligand;

Figure 3 schematically depicts preparation of a bidentate ligand according to the present invention by combining Salpen('Bu)[B(OMe)₂]₂ (1) and Salben('Bu)[B(OMe)₂]₂ (2) with a stoichiometric amount of BBr₃;

20 Figure 4 graphically shows a catalytic process for dealkylation of a phosphate ester according to the present invention; and

Figure 5 schematically depicts the formation of a cationic intermediate from a composition of the present invention.

Reference will now be made in detail to the presently preferred embodiments of the invention, examples of which are illustrated in the accompanying drawings.

Detailed Description of the Invention.

5 In accordance with one aspect of the present invention, the composition provided by the present invention may be a chelate having the general formula $L\{YX_m\}_n$, where Y is a Group 13 element, X is a halide, and L is a chelating ligand having a bidentate binding site comprising sites E and E' contacting the Group 13 element. E and E' may be O, N, P, S, or any
10 combination thereof. Both bidentate (Figure 1), quadridentate (Figure 2), and greater ligands are contemplated by the present invention. The compositions of the present invention show excellent activity in dealkylating various phosphates and ethers as will be shown herein. An additional advantage is that the method of the present invention may be conducted at room
15 temperature.

Other aspects of the present invention will become apparent to those skilled in this art from the following description wherein there is shown and described a preferred embodiment of this invention, simply by way of illustration of one of the modes best suited to carry out the invention. As it
20 will be realized, this invention is capable of other different embodiments and its several details are capable of modification in various, obvious aspects all without departing from the intended scope of the invention. Accordingly, the descriptions and examples herein will be regarded as illustrative in nature and

not as restrictive.

Example 1. Preparation of Salpen(^tBu)(BBr₂)₂

Binuclear boron bromides were prepared in high yields by combining Salpen(^tBu)[B(OMe)₂]₂ or Salben(^tBu)[B(OMe)₂]₂ with a stoichiometric amount of BBr₃. To a stirring solution of Salpen(^tBu)[B(OMe)₂]₂ (3.0 g, 4.62 mmol) in toluene (50 ml) was added 1 M BBr₃ in heptane (6.24 ml, 6.24 mmol). The reaction mixture was stirred for 24 hours, and the solvent removed. The remaining solid was washed with 10 ml of hexanes, and filtration and vacuum drying yielded 3.28 g (88% yield) Salpen(^tBu)(BBr₂)₂.

10 Example 2. Preparation of Salben(^tBu)(BBr₂)₂

To a stirring solution of Salben(^tBu)[B(OMe)₂]₂ (1.0 g, 1.51 mmol) in toluene (50 ml) was added 1 M BBr₃ in heptane (2.04 ml, 2.04 mmol). The reaction mixture was stirred for 18 hours at room temperature. The solution was concentrated to 10 ml, filtered, and dried. The yield was 0.96 g (76% yield) Salben(^tBu)(BBr₂)₂.

NMR analysis showed a broad single peak (at δ -0.57 and -0.40 ppm, respectively) for both binuclear boron bromide compounds prepared as described in Examples 1 and 2, upfield from a related chloride analogue Salpen(^tBu)[BCl₂]₂ (at δ 6.21 ppm).

20 Example 3. Dealkylation of Phosphates with Salpen(^tBu)(BBr₂)₂

Salpen(^tBu)(BBr₂)₂, prepared as described in Example 1, was evaluated

for its ability to dealkylate various phosphate esters. In a NMR tube, phosphate was added to an equimolar solution of Salpen(^tBu)(BBr₂)₂ in CDCl₃, and held at room temperature for 30 minutes. The reaction was monitored by ¹H NMR. As shown in Table 1, significant dealkylation, measured by the amount of phosphate remaining in the reaction mixture in comparison to the amount of alkyl bromide produced, could be achieved with the composition of the present invention.

Table 1. Percent dealkylation of phosphates with Salpen(^tBu)(BBr₂)₂

Phosphate	Conversion (%) ^a
(MeO) ₃ P(O)	89
(EtO) ₃ P(O)	63
(^t BuO) ₃ P(O)	99
(^t PentO) ₃ P(O)	98
(MeO) ₂ P(O)H	85
(MeO) ₂ P(O)Me	99
(^t PrO) ₂ P(O)H	63
(PhO) ₂ ((2-Et)HexO)P(O)	71
(Me ₃ SiO) ₃ P(O)	98
(PhO) ₃ P(O)	0

^a The percent conversion was determined by the amount of phosphate remaining to the amount of alkyl bromide produced in the ¹H NMR.

Example 4. Dealkylation of phosphates with binuclear boron compounds

Various binuclear boron compounds, synthesized substantially as described in Examples 1 and 2, were evaluated for dealkylation of phosphate esters as described in Example 3. For comparison, a positive control consisting of BBr_3 in CDCl_3 was used. As shown in Tables 2-5, the compounds of the present invention were effective in cleaving phosphate bonds for various phosphate compounds. In contrast, BBr_3 was ineffective (Table 5). Activity of the boron halide compounds of the present invention did not decrease with extension of the alkyl chain on the phosphates. 5 However, a slight decrease in activity of the compounds was observed with 10 the branched phosphates such as $(\text{PhO})_2((2\text{-Et})\text{HexO})\text{P}(\text{O})$.

Table 2. Dealkylation of phosphates by Salen ligands having the formula $L[BBr_2]_2$.

		Phosphate					
		$(MeO)_3P(O)$	$(EtO)_3P(O)$	$(n-BuO)_3P(O)$	$(MeO)_2P(O)Me$	$(PhO)_2P(O)$	$(MeSiO)_3P(O)$
		30 min.	24 hr.	30 min.	24 hr.	30 min.	24 hr.
5	Salen(t)	30	24	30	24	30	24 hr.
		min.	hr.	min.	hr.	min.	
	Salpen(t)	76	94	26	32	42	57
	Salben(t)	74	82	68	74	99	84
	Salhenn(t)	60	78	46	53	77	91
	Salhenn(t)	58	81	55	66	60	69

Table 3. Dealkylation of phosphates by Salen ligands having the formula $L[MePhBBr_2]_2$.

	$(MeO)_3P(O)$	Phosphate									
		$(EtO)_3P(O)$	$(n\text{-BuO})_3P(O)$	$(MeO)_2P(O)H$	$(MeO)_2P(O)Me$	$(i\text{-PrO})_2P(O)H$	$(PhO)_2P(O)(2\text{-ethylhexyl})$	$(MeSiO)_3PO$			
$L[MePhBBr_2]$	30 min.	24 hr.	30 min.	24 hr.	30 min.	24 hr.	30 min.	24 hr.	30 min.	24 hr.	30 min.
Salen(t)	45	62	40	98	31	46	59	67	47	56	42
Salpen(t)	52	69	50	64	58	75	67	82	64	69	32
Salbent(t)	92	83	71	98	70	99	50	82	50	63	37
Salhent(t)	80	88	56	98	47	98	50	76	42	66	26

Table 4. Dealkylation of phosphates by Salen ligands having the formula $L[B\text{Cl}_2]_2$.

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Phosphate				
	$(\text{MeO})_3\text{P}(\text{O})$		$(\text{MeSiO})_3\text{P}(\text{O})$	
$L[B\text{Cl}_2]_2$	30 min.	24 hr.	30 min.	24 hr.
Salen(t)	7	45	84	87
Salpen(t)	20	32	66	75
Salben(t)	11	53	81	84
Salhen(t)	7	47	57	63
Salpten(t)	42	62	73	86

Table 5. Dealkylation of phosphates by BBr_3 .

	Phosphate									
	$(\text{MeO})_3\text{P(O)}$	$(\text{EtO})_3\text{P(O)}$	$(\text{n-BuO})_3\text{P(O)}$	$(\text{MeO})_2\text{P(O)H}$	$(\text{MeO})_2\text{P(O)Me}$	$(i\text{-PrO})_2\text{P(O)H}$	$(\text{PhO})_2\text{P(O)H}$	(2-ethylhexyl)	$(\text{MeSiO})_3\text{P(O)}$	
	30 min.	24 hr.	30 min.	24 hr.	30 min.	24 hr.	30 min.	24 hr.	30 min.	24 hr.
BBr_3	1.1	3.4	0	2.7	5	0	1	12	2	2
B-Bromo	74	99	37	66	31	54	84	87	58	92
									76	84
									87	95
									99	99

^a B-Bromocatecholborane

Example 5. Catalytic process for dealkylating phosphates

Because Salpen('Bu)(BBr₂)₂ can be generated in situ from Salpen('Bu)[B(OMe)₂]₂ and BBr₃, the process can be made catalytic. The reaction is shown schematically in Figure 4. In a NMR tube, equimolar amounts of (MeO)₃P(O) and BBr₃ were added to a solution of Salpen('Bu)(BBr₂)₂ in CDCl₃ in the ratio of 20:1 of phosphate to borate and held at room temperature. The reaction was monitored by ¹H NMR. Dealylation of trimethyl phosphate occurred within five minutes. Dealylation (75% conversion) occurred within 30 minutes at a substrate to catalyst ratio of 200:1.

While not wishing to be bound by any theory, the mechanism may be one in which a cationic intermediate, which may be depicted in one embodiment of this invention as [(chelate)BBr]⁺, coordinates the P-O-C or C-O-C bond of a phosphate ester or ether, respectively, allowing a nucleophilic attack by the halide at the α -carbon. The reaction is depicted schematically in Figure 5, using a phosphate ester and a binuclear boron compound according to the present invention as an example. Accordingly, the present invention contemplates use of such cationic intermediates for dealylation of phosphate esters and ethers as described herein.

Example 6. Cleavage of MTBE

Methyl tertiary butyl ether was added to a CDCl₃ solution of binuclear boron ligands synthesized substantially as described in Examples 1 and 2 (4:1 ratio of MTBE:ligand). The solution was held at room temperature, and the

reaction monitored by ^1H NMR. Percent dealkylation was monitored by comparing the amount of methyl bromide produced to the amount of trimethyl phosphate remaining. As shown in Table 6, the compositions of the present invention are capable of dealkylating ethers as well as phosphate esters.

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Table 6. Cleavage of MTBE by bimetallic boron halide ligand.

Ligand	Conversion (%) ^a	
	30 min.	24 hr.
Salen('Bu)[BBr ₂] ₂	12	39.3
Salpen('Bu)[BBr ₂] ₂	3	10
10 Salben('Bu)[BBr ₂] ₂	5	25
Salhen('Bu)[BBr ₂] ₂	1	8

^a Percent dealkylation was determined by comparing the amount of methyl bromide produced to the amount of trimethyl phosphate remaining in the ^1H NMR.

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The foregoing description is presented for purposes of illustration and description of the various aspects of the invention. The descriptions are not intended to be exhaustive or to limit the invention to the precise form disclosed. The embodiments described above were chosen to provide the best illustration of the principles of the invention and its practical application to thereby enable one of ordinary skill in the art to utilize the invention in various embodiments and with various modifications as are suited to the

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particular use contemplated. All such modifications and variations are within the scope of the invention as determined by the appended claims when interpreted in accordance with the breadth to which they are fairly, legally and equitably entitled.